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Pattern of Response to Sofosbuvir and Daclatasvir +/- Ribavirin Regimen in Chronic Hepatitis C Patients

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ABSTRACT

Background: With the advent of direct-acting antivirals (DAAs) for hepatitis C virus (HCV), there has been a marked increase in the number of patients who achieve sustained virological response (SVR). Several factors mediate the response to therapy as immunologic and genetic factors.

Objective: We aimed to assess the pattern of response to sofosbuvir and daclatasvir +/- ribavirin regimen in chronic hepatitis C (CHC) patients and to study the predictors of non SVR (relapse).

Patients and methods: This prospective study was conducted on 506 consecutive HCV-infected patients. Abdominal ultrasonography, liver function tests, alpha-fetoprotein (AFP), HCV polymerase chain reaction (PCR), complete blood count (CBC), random blood glucose, C-X-C motif chemokine ligand 10 (CXCL10), Child-Pugh score, and some serum fibrosis indices were performed. After completion of the course of treatment, all patients were followed up for 6 months and then categorized into sustained virological responders and non-sustained virological responders (relapsers).

Results: Out of the 506 HCV-infected patients, 497 (98.2%) achieved SVR, and 9 (1.8%) experienced relapse. Response rates to sofosbuvir and daclatasvir +/- ribavirin in cirrhotic patients were lower than those without cirrhosis. The presence of liver cirrhosis (LC) and the need for receiving triple therapy were the main factors that predicted relapse in univariate analysis. CXCL10 levels showed statistically insignificant differences between responders and relapsers, between cirrhotic and non-cirrhotic patients, and between pretreatment and post-treatment levels.

Conclusions: Response rate of CHC patients to sofosbuvir and daclatasvir +/- ribavirin is excellent and relapse only occurred in a minority of patients (1.8%). Cirrhotic patients showed higher relapse rate than non-cirrhotic (55.65% *vs* 44.4%).

Keywords: CHC, CXCL10, DAAs, HCV, SVR.

INTRODUCTION

HCV infection is a major global public health burden with more than 71 million persons chronically infected[(1)]. In Egypt, nearly 5.3 million persons have HCV antibodies of whom, about 3.7 million individuals (69.5%) have CHC infection in 2015[(2)]. DAAs were considered the cornerstone of HCV management. The goal of antiviral therapy is to achieve SVR and to decrease liver-related deaths, hepatocellular carcinoma (HCC) rates, and liver-related complications[(3)].

SVR is defined as the absence of detectable HCV ribonucleic acid (RNA) in the serum for at least 24 weeks after the stoppage of treatment[(4)].

Successful treatment decreases the risk of HCC development by 75%[(5)]. Relapsers are those with undetectable HCV RNA in serum during treatment but then have a reappearance of HCV RNA in serum after discontinuation of treatment[(6)].

The predictors of response to therapy are related to the virus and host. During the era of interferon therapy, genotype was the strongest predictor of SVR[(7)]. In the era of DAAs, HCV genotype has a negligible role in predicting treatment response given the high efficacy of different DAA combinations against all genotypes[(8)]. When peginterferon and ribavirin (PEG and RBV) were used, there was a 9% lower chance of cure when the baseline HCV RNA level was over 2 million IU/Ml[(9)]. In the era of DAAs, the baseline HCV RNA has little impact on achieving SVR[(10)].

With interferon-based therapy, older age was associated with poor tolerance and a lower cure rate. In contrast, DAA therapy in the elderly is well tolerated and the SVR rate is similar to those in younger patients[(11)].

Factors associated with failure of DAA therapy include male gender, LC, null responders to previous PEG and RBV treatment, short-term regimens, poor adherence to treatment, and not giving ribavirin[(12)]. Genetic factors and liver fibrosis at the start of treatment, favor the appearance of resistance[(13)].

CXCL10 is involved in the pathogenesis of acute and chronic HCV infection. It predicts the first days of HCV RNA elimination during therapy. DAAs-mediated clearance of HCV is associated with a significant decrease in this chemokine[(14)].

We aimed to assess the pattern of response to sofosbuvir and daclatasvir +/- ribavirin regimen in CHC patients and to study the predictors of non SVR (relapse).

PATIENTS AND METHODS

This prospective study was conducted on 506 consecutive HCV-infected patients attending Tropical Medicine and Gastroenterology Outpatient Clinic, Sohag University Hospital. All patients were advised to receive sofosbuvir and daclatasvir +/- ribavirin regimen in a specialized center in the period from April 2018 to April 2019. The patients were eligible for treatment of HCV according to the Modified National Program for the Treatment of HCV in Egypt. Complete medical history and clinical examination were performed for all patients.

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Patients with HCV and hepatitis B virus (HBV) co-infection or HCC and patients with chronic renal failure were excluded. Body mass index (BMI) was calculated and abdominal ultrasonography was done for all patients. Liver function tests and CBC were performed pretreatment; and at the 4th, 8th, and 12th weeks of treatment. Pretreatment AFP and random blood glucose were performed for all patients. Glycosylated hemoglobin (HbA_1C) was performed for diabetic patients. Child-Pugh score[15], the model for end-stage liver disease (MELD) score[16], aspartate aminotransferase to platelets ratio index (APRI), fibrosis-4 (FIB-4) index[17] were determined, and fibroscan was done to all patients.

Before treatment, patients were categorized into:

(1) Chronic HCV-infected patients with LC (compensated or decompensated), classified according to Child-Pugh score.

(2) Chronic HCV-infected patients without LC.

The following drug regimens were given to the patients:

(1) The cirrhotic patients received sofosbuvir 400 mg plus daclatasvir 60 mg plus ribavirin 600 mg for 12 weeks.

(2) Non-cirrhotic patients received sofosbuvir 400 mg plus daclatasvir 60 mg for 12 weeks.

After completing the course of treatment, all patients were followed up for 6 months and then categorized into sustained virological responders and non-sustained virological responders (relapsers).

PCR of HCV RNA was assayed using the Roche COBAS AmpliPrep/COBAS TaqMan HCV Test. This test was performed pretreatment, at the end of the treatment, and at the 12th and 24th-week post-treatment. Serum samples were taken before and after treatment from random samples of patients then frozen at -80°C, to measure CXCL10 using interferon-gamma induced protein 10 (IP-10) Quantikine ELISA test.

Ethical consent:

An approval of the study was obtained from Sohag University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data were analyzed using SPSS version 18. Quantitative data were expressed as mean ± standard deviation (SD). Data were tested for normality using the Shapiro-Wilk test. Independent samples T-test was used for normally distributed data. The Mann–Whitney test was used for data that weren't normally distributed. Friedman test with multiple pair-wise comparisons was used for comparison between repeated measurements of the studied patients. Qualitative data were expressed as numbers and percentages and were compared by Fisher's exact test. P-value <0.5 was considered statistically significant.

RESULTS

Out of the 506 HCV-infected patients, 497 (98.2%) achieved SVR (responders), and 9 (1.8%) experienced relapse (relapsers). The main side effects of sofosbuvir and daclatasvir +/- ribavirin regimen were fatigue, headache, and anorexia (Table 1).

Table (1): Adverse effects of sofosbuvir and daclatasvir +/- ribavirin regimen in the studied patients

Side effects of treatment	N= 506
Fatigue	506 (100%)
Headache	322 (63.64%)
Anorexia	161 (31.82%)

We found statistically insignificant differences between responders and relapsers regarding age, gender, BMI, baseline liver function tests, AFP, baseline PCR, CBC, creatinine, random blood glucose, HbA1c, CXCL10, MELD score, APRI, FIB-4 index, and the results of fibroscan (Table 2).

Relapse was significantly more frequent in cirrhotic patients than non-cirrhotic. At the 4th week, mean alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, were significantly lower in responders than relapsers and at the 8th week mean ALT level was significantly lower in responders than relapsers (Table 2 and Figure 1).

Child-Pugh score was significantly lower in responders than relapsers. Relapse was significantly more frequent in patients who received triple therapy than those who received dual therapy for 3 months (Table 2).

Table (2): Relation between some variables and response to sofosbuvir and daclatasvir +/- ribavirin regimen

Variables	Responders (N=497) (Mean± SD) or N (%)	Relapsers (N=9) (Mean± SD) or N (%)	P-value
Age	53.97 ± 14.12	55.67 ± 4.64	0.857
Gender: Male	248 (49.9%)	7 (77.8 %)	0.176
Female	249 (50.1%)	2 (22.2%)	
Body mass index	27.69 ± 4.63	29.59 ± 2.06	0.220
Abdominal ultrasonography: Cirrhotic	122 (24.5%)	5 (55.6%)	**0.048**
Non-cirrhotic	375 (75.5%)	4 (44.4%)	
Total bilirubin (mg/dl): At baseline	0.6 ± 0.19	0.6 ± 0.19	0.682
At 4th week	0.71 ± 0.3	0.77 ± 0.54	0.912
At 8th week	0.78± 0.28	0.79 ± 0.48	0.917
Serum albumin (g/dl): At baseline	3.94 ± 0.48	3.71 ± 0.65	0.158
At 4th week	3.88 ± 0.36	3.67 ± 0.59	0.088
At 8th week	3.86 ± 0.29	3.73 ± 0.35	0.185
Alanine aminotransferase (U/ml): At baseline	59.02 ± 9.91	54.89 ± 2.65	0.687
At 4th week	21.65± 1.89	27.33 ± 2.31	**0.035**
At 8th week	15.22 ± 3.55	22.33 ± 5.9	**0.004**
Aspartate aminotransferase (U/ml): At baseline	65.21± 6.09	68.56 ± 7.09	0.313
At 4th week	28.69 ± 5.81	39 ± 7.36	**0.055**
At 8th week	24.56 ± 1.11	24.56 ± 1.11	0.062
International normalized ratio (%)	1.1 ± 0	1.1 ± 0	1
Alpha-fetoprotein (ng)	6.82 ± 1.77	6.88 ± 1.77	0.512
Baseline PCR (IU/ml)	2622366.3±51576.27	1886583.67 ± 17620.64	0.684
White blood cells (10^3/µl): At baseline	6.78 ± 1.25	6.11 ± 1.48	0.423
At 4th week	7.08 ± 1.34	6.96 ± 1.26	0.903
At 8th week	6.96 ± 1.12	6.58 ± 1.98	0.595
Hemoglobin (g/dl): At baseline	14.56 ± 1.67	14.41 ± 1.85	0.790
At 4th week	14.42 ± 2.71	13.7 ± 1.29	0.731
At 8th week	14.12 ± 3.81	13.34 ± 1.26	0.466
Platelets (10^3/µl): At baseline	220.14 ± 7.72	188.3 ± 7.49	0.225
At 4th week	230.54 ± 8.95	191.44 ± 6.73	0.194
At 8th week	228.49 ± 7.14	185.44 ± 6.01	0.078
Creatinine (mg/dl): At baseline	0.92 ± 0.21	0.86 ± 0.17	0.395
At 4th week	0.99 ± 0.19	1± 0.29	0.784
At 8th week	1.03 ± 0.2	0.99±0.18	0.786
Random blood glucose (mg/dl)	136.004 ± 7.58	131.56 ± 5.49	0.774
Glycosylated hemoglobin (%): Baseline	7.64 ± 1.67	6.1 ± 1.31	0.242
At the end of treatment	7.71 ± 1.89	6 ± 1.12	0.185
Pretreatment C-X-C motif chemokine ligand 10	136.55 ± 54.51	125.83 ± 16.27	0.207
Child-Pugh score for cirrhotic patients:			
Class A	113 (92.6%)	1 (20%)	
Class B	9 (7.4%)	3 (60%)	**<0.001**
Class C	0 (0.0%)	1 (20%)	
MELD score for cirrhotic patients	5.19 ± 2.93	4.4 ±3.39	0.563
Aspartate aminotransferase to platelet ratio index	0.87 ± 1.05	1.04 ± 0.72	0.188
Fibrosis 4 index	2.53 ± 2.49	3.46±2.39	0.145
Fibroscan: Stage 0	129 (26.0%)	0 (0.0%)	
Stage 1	120 (24.1%)	1 (11.1%)	
Stage 2	106 (21.4%)	2 (22.2%)	0.109
Stage 3	31 (6.2%)	1 (11.1%)	
Stage 4	111 (22.3%)	5 (55.6%)	
Treatment: Dual therapy for 3 months	382 (76.9%)	4 (44.4%)	
Triple therapy for 3 months	115 (23.1%)	5 (55.6%)	**0.038**

PCR: polymerase chain reaction, MELD: model for end-stage liver disease.

Note: glycosylated hemoglobin was done for 87 diabetic patients, and the C-X-C motif chemokine ligand 10 was done for 74 responders and 9 relapsers.

There was a statistically insignificant difference between cirrhotic and non-cirrhotic patients regarding baseline CXCL10 (Table 3).

Table (3): Comparison between cirrhotic and non-cirrhotic patients regarding baseline CXCL10

	Cirrhotic (N=37) (Mean± SD)	Non-cirrhotic (N=46) (Mean± SD)	P-value
Baseline C-X-C motif chemokine ligand 10	133.33 ± 40.21	137.96 ± 63.85	0.702

We compared baseline and post-treatment CXCL10 levels in 10 responders and found a statistically insignificant difference between them. Also, we compared baseline and post-treatment HbA1c levels in 87 responders. We found that the mean post-treatment HbA1c level was significantly lower than its baseline level (Table 4).

Table (4): Comparison between baseline and post-treatment CXCL10, and HbA1c in responders

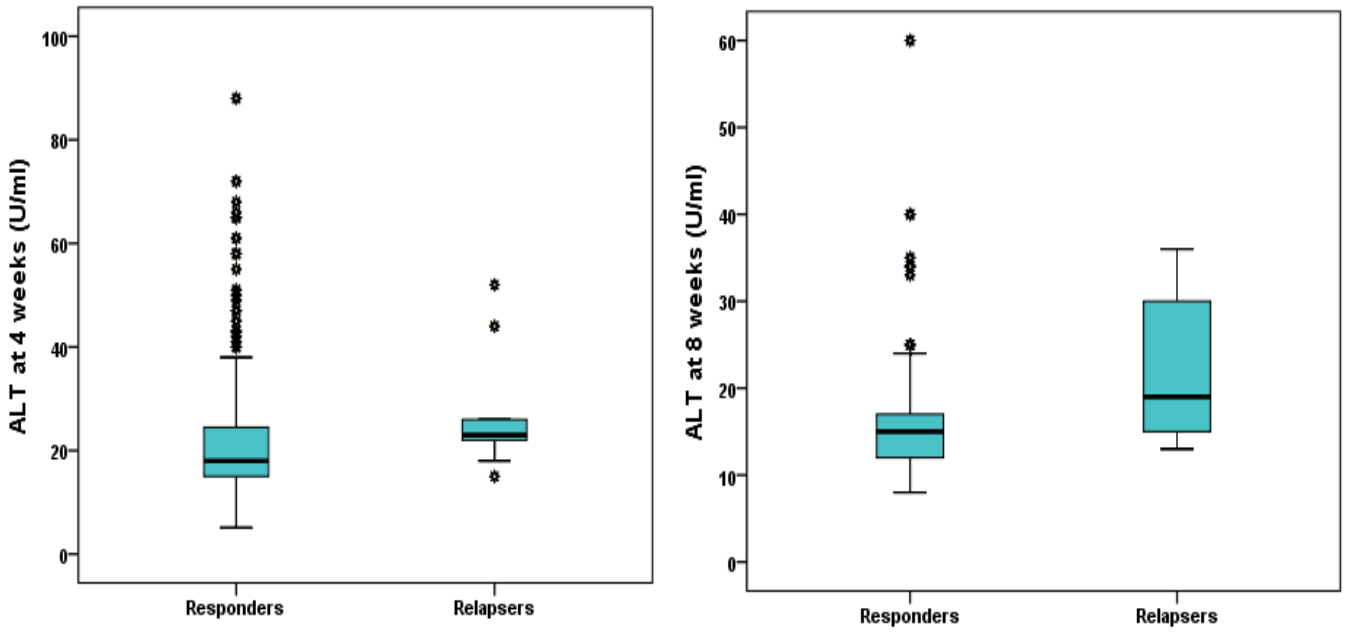
Variables	Baseline (Mean± SD)	Post-treatment (Mean± SD)	P-value
C-X-C motif chemokine ligand 10 (N=10)	94.9 ± 82.99	93.75 ± 44.83	0.959
Glycosylated hemoglobin (N=87)	7.71 ± 1.89	7.64 ± 2.67	**0.02**

Univariate and multivariate binary logistic regression analyses of predictors of relapse after sofosbuvir and daclatasvir +/- ribavirin were done and we found that the presence of LC and the need for receiving triple therapy were the main factors that predicted relapse in univariate analysis. However, this result couldn't be confirmed in multivariate analysis (Table 5).

Table (5): Univariate and multivariate binary logistic regression analysis of predictors of relapse after sofosbuvir and daclatasvir +/- ribavirin regimen

Characteristics	Odds ratio (Confidence interval 95%)	P-value
Univariate analysis		
Age	1.01 (0.96 -1.06)	0.719
Gender: Male Female	1 0.28 (0.06 - 1.38)	0.119
Body mass index	1.08 (0.95 - 1.23)	0.223
Cirrhosis: Yes No	3.84 (1.02 -14.54) 1	**0.047**
Total bilirubin (mg/dl)	0.99 (0.11 - 9.21)	0.99
Serum albumin (g/dl)	0.38 (0.1 - 1.43)	0.153
Alanine aminotransferase (U/ml)	0.99 (0.98 - 1.02)	0.757
Aspartate aminotransferase (U/ml)	1.01 (0.99 - 1.02)	0.828
Alpha-fetoprotein (ng)	1.002 (0.88 - 1.14)	0.971
Baseline PCR (IU/ml)	1 (1 - 1)	0.688
White blood cells (10^3/µl)	0.86 (0.62 - 1.19)	0.382
Hemoglobin (g/dl)	0.95 (0.64 - 1.4)	0.793
Platelets (10^3/µl)	0.99 (0.98 - 1.003)	0.191
Creatinine (mg/dl)	0.2 (0.01 - 5.87)	0.353
Random blood glucose (mg/dl)	0.99 (0.98 - 1.01)	0.857
Glycosylated hemoglobin (%)	0.83 (0.43 - 1.57)	0.559
C-X-C motif chemokine ligand 10 (ng)	0.99 (0.98 - 1.01)	0.556
Child-Pugh score: Class A Class B Class C	1 3.77 (0.36 - 40.15) 5.5	 0.27 1
MELD score	0.93 (0.66 - 1.23)	0.659
Aspartate aminotransferase to platelet ratio index	1.13 (0.71 - 1.79)	0.618
Fibrosis 4 index	1.09 (0.93 - 1.27)	0.283
Treatment: Dual therapy for 3 months Triple therapy for 3 months	1 4.15 (1.09 -15.72)	 **0.036**
Multivariate analysis		
Cirrhosis: Yes No	1.39 (0.05 -39.08) 1	0.846
Treatment: Dual therapy for 3 months Triple therapy for 3 months	1 3.07 (0.11 - 86.09)	 0.51

PCR: polymerase chain reaction, **MELD:** model for end-stage liver disease.



(A) **(B)**

Figure (1): Comparison between responders and relapsers regarding ALT. Responders show significantly lower ALT at the 4th week (A), and the 8th week (B) compared to relapsers. The black lines show comparisons between groups at a time point, and the blue boxes show differences in fold change between groups over time.

DISCUSSION

HCV is a major public health concern. The presence of effective DAA therapy provides an effective cure for HCV patients who were previously ineligible for treatment[18]. The predictors of response to therapy are related to the virus and host, and they can be classified as immunologic and genetic factors[19].

In our study, we found that 98.2% of the patients achieved SVR and 1.8% experienced relapse. This higher rate of SVR could be explained by the fact that the majority of our patients had compensated liver disease. Our result was better than that of **Childs *et al.*** [20] who found 75% of patients achieved SVR, and 25% experienced relapse after the end of treatment.

We found that the most common side effects associated with sofosbuvir and daclatasvir +/- ribavirin regimen were fatigue, headache, and anorexia. **Stedman**[21] found that the most common side effects associated with ribavirin therapy were fatigue, insomnia, and anemia. Others found that only 19.7% of patients reported minor side effects mainly fatigue, anemia, headache, and insomnia[22]. Headache was also frequently reported by **Gane *et al.*** [23].

We found statistically insignificant differences between responders and relapsers regarding age and gender. This was in agreement with **Childs *et al.*** [20]**. Rheem *et al.*** [11] found that DAA therapy in older patients is well tolerated and SVR rates are similar to those seen in younger patients. In contrast, some authors found that younger patients (age <40) had higher SVR due to better immunological conditions, less chronic diseases, and less medications when compared to older patients[9, 24]. **Lanini *et al.*** [25] found that females achieved higher SVR than males; however, whether a causal biological link stands behind this association was unclear.

We found an insignificant difference in BMI between responders and relapsers. A similar result was reported by **Lanini *et al.*** [25]**.** In contrast, others found that patients with high BMI especially ≥ 40 had a higher risk of relapse[26].

Our study revealed that cirrhosis was significantly higher in relapsers than responders. This agrees with **Lanini *et al.*** [25] who found that SVR12 was 96% in patients without cirrhosis compared to 77% in those with cirrhosis.

In our study, we found that baseline ALT levels didn't differ significantly between responders and relapsers. We found that the reduction in ALT levels at the 4th week and 8th week in comparison to baseline levels was more significant in responders than relapsers that could be explained by the improvement of hepatic inflammation with treatment. Some authors found that patients with higher levels of baseline ALT were more likely to normalize after treatment, suggesting that the presence of active HCV-induced hepatitis is more likely to be reversed[27]. Others found that ALT levels were normalized in more than 75% of patients with SVR and in about 50% of relapsers[25].

We found an insignificant difference in baseline HCV RNA between responders and relapsers. This was in agreement with many authors[10, 20]. However, some authors found that HCV viral load >6 million IU/ML was associated with failure to achieve SVR12[28].

We found an insignificant difference in baseline HbA1c level between responders and relapsers. In contrast, **McCaughan and George**[29] found that insulin resistance is important in determining the outcome of HCV treatment as there is a significant correlation between insulin resistance and the degree of hepatic fibrosis. Others found that diabetes mellitus (DM) was independently associated with failure to achieve SVR12[28].

We found an insignificant difference in baseline CXCL10 between responders and relapsers. In contrast, **Childs *et al.*** [20] found that relapsers had higher baseline CXCL10 levels compared to responders, and explained this by the different immunological characteristics of responders and relapsers. Others found that low pretreatment levels of CXCL10 both in the liver and plasma were associated with a marked first-phase reduction of HCV loads for all viral genotypes, and were associated with SVR for genotypes 1 and 4[24].

In cirrhotic patients, we found a significant difference in Child-Pugh score between responders and relapsers, where most of the responders were in class A and most of the relapsers were in class B. Thus the degree of liver dysfunction appeared to affect SVR in Child-Pugh scores B and C. In contrast, others found that the Child-Pugh score showed an insignificant difference between responders and relapsers[20].

We found an insignificant difference in MELD score between responders and relapsers. This was in agreement with **Childs *et al.*** [20]. In contrast, **El-Sherif *et al.*** [30] found that higher MELD categories of 12-14, were associated with lower ratios of clinical improvement compared to MELD categories of less than 12.

We found insignificant relation between fibrosis and response to treatment. In contrast, others found that the first-phase decline in HCV RNA is dependent on the decrease in fibrosis stage[31]. **Patel *et al.*** [28] found that less fibrotic liver (FIB-4 score <1.45) was more likely to achieve SVR12 while FIB-4 score >3.25 was associated with treatment failure.

We found that the relapse was significantly more in cirrhotic patients who needed triple antiviral therapy. Similarly, **Patel *et al.*** [28] found that triple antiviral therapy for cirrhotic patients was associated with treatment failure.

CXCL10 levels showed statistically insignificant differences between cirrhotic and non-cirrhotic patients, and between pretreatment and post-treatment levels. This might be due to the small number of cases or due to the measurement of CXCL10 shortly after treatment. In contrast, **Spaan *et al.*** [32] found a significant decrease in post-treatment CXCL10 measures in all patients after receiving DAAs.

Our results revealed that post-treatment HbA1c levels were significantly lower than pretreatment levels and we explained this by that diabetic patients were adherent to antidiabetic treatment, and the cure of CHC was associated with better control of DM. This was in agreement with **Pavone *et al.*** [33] who found a rapid decline of fasting blood glucose and HbA1c in diabetic patients treated with DAA agents. In contrast, **Stine *et al.*** [34] found that HbA1c was largely unaffected by receiving DAAs in cirrhotic or non-cirrhotic patients.

In the univariate analysis, we found that cirrhosis and the need for triple antiviral therapy were significant predictors of relapse after receiving sofosbuvir and daclatasvir +/- ribavirin regimen. However, this result couldn't be confirmed in multivariate analysis.

CONCLUSION

Response rate of CHC patients to sofosbuvir and daclatasvir +/- ribavirin is excellent and relapse only occurred in a minority of patients (1.8%). Cirrhotic patients showed higher relapse rate than non-cirrhotic (55.65% *vs* 44.4%).

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